

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 6

REMARKS

Claims 1-8 are pending in the subject application. By this Amendment, applicants have amended claims 1-8 and added claim 9. No issue of new matter is raised by these amendments. Claim 1 has been amended to make certain formatting changes and to more specifically describe the solution of the claimed process. Support for the amendment of claim 1 may be found in the specification at page 3, line 30 to page 4, line 32, page 10, line 28, Example 1, page 11, line 6, Example 2, and line 25, Example 3, page 12, line 3, Example 4, line 18, Example 5, and line 29, Example 6, page 13, line 10, Example 7, and line 21, Example 8, page 14, line 3, Example 9, line 14, Example 10, and line 29, Example 11, and page 15, line 6, Example 12. Claims 2-7 have been amended for proper dependency language. Claim 5 has also been amended to properly describe the R groups of the quaternary ammonium salt of the claimed process. Support for the amendment of claim 5 may be found in the specification at page 5, lines 10-17. Support for new claim 9 may be found in the specification at page 4, lines 23-29, page 11, lines 13-14, and page 13, lines 27-28. Claims 1-8 as amended and new claim 9 will be pending in the subject application upon entry of this Amendment.

In view of the arguments below, applicants maintain that the grounds of the Examiner's rejections have been

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 7

overcome, and respectfully request that these grounds of rejection be withdrawn.

### Priority

The Examiner acknowledges applicants' claim for foreign priority based on an application filed in India on October 31, 2003. The Examiner alleges, however, that applicants have not filed a certified copy of the Indian application as required by 35 U.S.C. §119(b).

In response, applicants contend that a certified copy of the priority document, i.e. Indian Patent Application No. 1148/Mum/2003, was submitted to the U.S. Patent and Trademark Office on July 14, 2004. Applicants attach hereto as **Exhibit A**, a copy of the postcard receipt listing the certified copy of Indian Patent Application No. 1148/Mum/2003 and stamped received by the U.S. Patent and Trademark Office on July 16, 2004 as prima facie evidence of receipt by the U.S. Patent and Trademark Office of the certified copy Indian Patent Application No. 1148/Mum/2003 (M.P.E.P. §503). However, during an April 12, 2005 telephone conference between Examiner Kumar and Ms. Aude Gerspacher of the undersigned attorney's office, Examiner Kumar indicated that although the transmittal letter forwarding the certified copy of the priority document was received, the priority document itself appears to have been lost in the Patent Office. The Examiner requested that

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 8

another certified copy of the Indian application be filed. Accordingly, applicants are seeking to obtain a new certified copy of the priority document for filing.

**Rejection Under 35 U.S.C. §112, Second Paragraph**

In the January 19, 2005 Office Action, the Examiner rejected claims 7-8 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleged that these claims depict chlorohydrin as formula (5), but there is no formula (5) anywhere in claim 1, thus rendering these claims indefinite.

In response, applicants note that amended claims 7 and 8 no longer refer to formula (5). Applicants also maintain that chlorohydrin, depicted as formula (5), is both known in the art and described in the specification at page 9, lines 11-16. Accordingly, applicants maintain that amended claims 7 and 8 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that this ground of rejection be reconsidered and withdrawn.

**Rejection Under 35 U.S.C. §103(a)**

The Examiner in the January 19, 2005 Office Action rejected claims 1-8 under 35 U.S.C. §103(a) as allegedly

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 9

unpatentable over JP 04-198175 (JP'175) or JP 01-102072 (JP'072).

The Examiner stated that the instant claims are directed to a process of making atenolol, by reacting a phenol with epichlorohydrin in the presence of alkali metal hydroxide and a quaternary ammonium salt as phase transfer catalyst, wherein an intermediate glycidyl ether is formed, which is then reacted with isopropylamine to give atenolol.

The Examiner also stated that JP'175 or JP'072 teach a process of making atenolol, by reacting a phenol with epichlorohydrin in the presence of alkali metal hydroxide and a quaternary ammonium salt as phase transfer catalyst, wherein an intermediate glycidyl ether is formed, which is then reacted with isopropylamine to give atenolol. The Examiner further stated that the differences between the references and the claimed process appears to be the temperature range and amount of the reactants and catalyst.

The Examiner alleged that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the process of JP'175 or JP'072, to make atenolol, by reacting a phenol with epichlorohydrin in the presence of alkali metal hydroxide and a quaternary ammonium salt as phase transfer catalyst, wherein an intermediate glycidyl ether is formed, which is then reacted with isopropylamine, because the prior art is

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 10

expressly teaching all the steps and the process is analogous with any difference being with respect to the temperature range and amount of the reactants, which can be worked out under routine experimentation, with a reasonable expectation of achieving a high yield of purified atenolol, absent evidence to the contrary.

In response to the Examiner's grounds of rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three basic criteria with respect to each claim. First, the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would have resulted.

In light of these requirements, applicants maintain that the cited references fail to support a *prima facie* case of obviousness for claims 1-8.

Claims 1-8 provide an improved process for the preparation of (S)-atenolol which results in high yields of optically active (S)-atenolol with optical purity of >99% ee.

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 11

The cited references fail to teach all elements of the instant methods. In particular, and as the Examiner acknowledges on page 4 of the January 19, 2005 Office Action, the temperature range of  $-10^{\circ}\text{C}$  to  $0^{\circ}\text{C}$  which is specified in step (a) of applicants' claimed process is not taught by either JP'175 or JP'072.

Moreover, the resulting high yield and purity of (S)-atenolol is based on applicants' surprising discovery that a temperature of above  $0^{\circ}\text{C}$  lowers the optical purity of the (S)-atenolol intermediate of formula (4). Applicants discovered that during the course of the reaction, if the reaction temperature rises above  $0^{\circ}\text{C}$ , the phenoxide anion attacks the C-1 carbon atom of (R)-epichlorohydrin with the expulsion of chloride to yield (R)-glycidyl ether, which on reaction with isopropyl amine gives (R)-atenolol, i.e. the original epoxide ring remains unchanged if the temperature rises above  $0^{\circ}\text{C}$ . When the temperature is lowered below  $0^{\circ}\text{C}$ , the attack of the phenoxide ion takes place to produce (S)-atenolol intermediate (4) with the desired purity. This sequence of attack is disclosed on page 8 of the instant specification.

Applicants disagree that the selection of the claimed temperature range would have been obvious to one skilled in the art by routine experimentation for improving yield and optical purity. Specifically, applicants maintain there is no indication in either JP'175 or JP'072 that higher yields

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 12

of optically active (S)-atenolol were desirable or achievable at all, let alone by using a lower temperature. In fact neither process results in high yields or optical purity of >99% ee. JP'175 describes a process for the preparation of (S)-atenolol which results in a 72.2% yield and an optical purity of 94.8%; JP'072 describes a process which results in an overall yield of 58% of racemic atenolol. Furthermore, applicants maintain that the claimed process differs from the process of JP'175 in that it is carried out in water only, not in aqueous organic solvents.

Applicants further maintain that their two-step claimed process differs from the one-step process of JP'175 in that the claimed process produces a mixture of glycidyl ether and chlorohydrin, while only the glycidyl ether is produced by the process of JP'175. Applicants also maintain that their claimed process for the preparation of (S)-atenolol differs from the process of JP'072 for preparation of racemic atenolol. Applicants set forth below **Tables 1 and 2** which compare and contrast the claimed process and each of JP'175 and JP'072.

Applicants: Satish Ramanlal Mehta et al.  
 Serial No.: 10/701,942  
 Filed : November 5, 2003  
 Page 13

Table 1: Comparison of the process and resulting product disclosed in JP 04-198175 A and the process and resulting product claimed in the subject application

	Process and resulting product as disclosed in JP04-198175 A	Process and resulting product claimed
1	Reaction carried out in aqueous organic solvents	Reaction carried out solely in water.
2	Reaction carried out at above +5°C	Reaction temperature is -10 to 0°C.
3	Only the glycidyl ether is obtained by reaction of para hydroxyl phenyl acetamide and optically active epichlorohydrin	A mixture of the glycidyl ether and compound (5) in a ratio between 3:2 and 7:3 is obtained.
4	One pot reaction for preparation of (S)-atenolol.	Two step reaction which gives better optical purity and yield of (S)-atenolol.
5	Yield of (S)-atenolol: 72.2%. <b>Note:</b> There is no improvement in yield even after being a one pot reaction.	Yield of (S)-atenolol: 77.4%. Yield is higher, even though it is a two step reaction.
6	Optical purity: 94.8%(ee)	Optical purity: 99.1%(ee). Purity is higher by 4%.

Table 2: Comparison of the process and resulting product disclosed in JP 01-102072 A and the process and resulting product claimed in the subject application

	Process and resulting product disclosed in JP 01-102072 A	Process and resulting product claimed
1	This method is for the preparation of racemic atenolol and not optically active (S)-atenolol.	This method is only for the preparation of (S)-atenolol.
2	Reaction is carried out at a higher temperature of 65-66°C and further at 70-72°C.	Reaction is carried out at a low temperature which is -10 to 0°C.
3	Overall Yield is only 58%.	Overall Yield is 77.4%. Yield is significantly higher.
4	Racemic atenolol is obtained. (No optical purity)	Optically pure (S)-atenolol with purity greater than 99% is obtained.



Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 14

Applicants maintain that, for the reasons above, the cited references even in combination fail to disclose all of the elements of their claimed process and therefore do not and cannot render obvious their claimed process. Furthermore, absent the teachings in the subject specification regarding the temperature range from which high yield and high optical purity results, no reasonable expectation of success in achieving such yield and purity existed. Routine optimization experimentation in the prior art did not point to the claimed temperature range, as evidenced by the lack of any teaching of the claimed temperature range or of varying the range in either JP'175 or JP'072. Accordingly, applicants maintain that the Examiner has failed to set forth a *prima facie* case of obviousness, that in any event an unexpected and surprising result is achieved by applicants' claimed process, and therefore claims 1-8 are not subject to rejection under 35 U.S.C. §103(a).

#### Summary

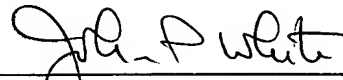
In view of the amendments and arguments set forth above, applicants maintain that the grounds of the Examiner's rejections set forth in the January 19, 2005 Office Action have been overcome. Applicants respectfully request that the Examiner reconsider and withdraw these grounds of rejection, and solicit allowance of the claims now pending.

Applicants: Satish Ramanlal Mehta et al.  
Serial No.: 10/701,942  
Filed : November 5, 2003  
Page 15

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

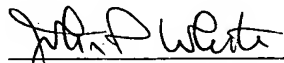
Respectfully submitted,



John P. White, Esq.  
Registration No. 28,678  
Attorneys for Applicants  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, NY 10036  
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

 4/19/05

John P. White Date  
Reg. No. 28,678